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Letter: hepatitis B surface seroclearance does reduce the risk of hepatocellular carcinoma - authors' reply

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Sirs, We appreciate the interest in our study from Professors Chen and Liaw and the opportunity to provide additional information.[1] As we acknowledged in our paper, the wide confidence intervals for our risk estimates resulting from the relatively small number of case- and control-patients developing HCC were an important limitation to our study.[2] Thus, it is possible that we failed to detect a real reduction in HCC risk because of insufficient statistical power. As requested, we recalculated the risk for developing HCC after excluding the 2 case-patients who received antiviral treatment before HBsAg seroclearance and the 32 control-patients who had received antiviral treatment. After adjusting for age at cohort entry and initial anti-hepatitis B e antibody status, we did not detect a difference in HCC risk among case-compared with control-patients after excluding patients who had received antiviral treatment (adjusted hazard ratio: 0.7; 95% confidence interval: 0.2–2.7). The effect of age at HBsAg seroclearance on risk for HCC is complex and could be partly related to the specific HBV genotypes represented in a population. It has been demonstrated that the duration of hepatitis B e antigen persistence and the risk for HCC is substantially higher for persons with HBV genotype C compared with other genotypes.[3,4] The majority of patients in the study indicating an increased risk for HCC among persons aged ≥50 years at the time of HBsAg seroclearance were infected with HBV genotype C.[5,6] In contrast, the majority of patients in our study population were infected with HBV genotype D. Therefore, the risk for HCC associated with a later age of HBsAg seroclearance among Alaska Native persons compared with other geographic regions is unclear because of differences in the prevalence of HBV genotypes. Furthermore, the age at HBsAg seroclearance should not affect our interpretation of the relative risk for HCC between case- and control-patients because the majority of participants acquired HBV infection in early childhood and our analysis adjusted for case-patients' HBsAg duration prior to seroclearance. We also speculated in our paper that ongoing low-level HBV DNA replication with continued integration into the host hepatocyte could have contributed to persistent HCC risk after HBsAg seroclearance. Further study is necessary to determine the relative importance of HBV viremia early in the

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course of disease versus persistence of viremia after HBsAg clearance in the development of HCC.

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